Claims 1-11 are pending in this application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(1) The claims recite several instances of "previous day's dose was held" or variation thereof (emphasis added). This could mean held unchanged or withheld. Since alternative interpretations are so opposite in effect, clarification is needed.

(2) The claims are drawn to a complicated schematic with multiple nested and related if-then type clauses. The problem is that the choices do not cover all scenarios.

In claim 2, there are three choices for day 1 dose of efaproxiral sodium: 100, 75 or 0 mg/kg. However, for one of these three doses to be chosen, certain conditions must be met. The problem here is that the conditions set forth in the claims do not cover all possibilities. For example, what if the patient's SpO_2 is 92.1% to 92.9%? The claims do not address such a patient. Hence, the claims are unclear and indefinite as to the efaproxiral sodium dose.

Also, numerous situations are unclear for days 2-10 (these are non-limiting examples, merely illustrative of the claim indefiniteness):

- Previous dose was 100 mg/kg, SpO_2 is >90%, and an adverse event not listed by applicant occurred on day 1. It is not clear if (2)(B)(i)(d) or (2)(B)(ii)(f) should be

literally followed by further administering potentially toxic 100 mg/kg or 75 mg/kg since an adverse event has occurred, albeit one that is not specifically covered by the Markush group(s).

- If the previous dose was 75 mg/kg, SpO_2 is now >90%, and an adverse not covered by (2)(B)(ii)(g) or (2)(B)(iii)(b) occurs, it is unclear which dose should be chosen.

- If a patient has SpO_2 ≥93% and the previous day's dose was 75 mg/kg with no adverse event (or an adverse event not covered by the claim language occurred), both (2)(B)(i)(c) and (2)(B)(ii)(g) would apply. It is unclear which dose should be chosen.

- If the previous day's dose was withheld (0 mg/kg), SpO_2 is 92.1% to 92.9%, and no adverse event occurs, it is unclear which does should be chosen.

Similar problems of incompleteness are noted also in claim 3:

- If dose on day 1 was 0 mg/kg, wherein no adverse event occurred on day 1, and SpO_2 is now ≥90% + creatinine is <2.0 mg/dL, it is unclear which dose should be chosen.

- If the previous day's dose was 75 mg/kg, SpO_2 is >90%, and an adverse event not listed in (B)(i)(c) occurred on the previous day, it is unclear which does should be chosen. Since the adverse event may be serious, continuing the potentially toxic 75 mg/kg as literally possible from the claim in (B)(i)(c) is indefinite without additional guidance.

- If the previous dose was 75 mg/kg, there has been no occurrence of an adverse event, and SpO_2 is >90% but creatinine is >2.0 mg/dL, it appears that both (B)(i)(c) and (B)(iii)(b) apply. It is unclear which dose should be chosen.

- (B)(i)(c) and (B)(ii) cover many of the same situations. (B)(ii) does not exclude its conditions from (B)(i)(c). So it is unclear whether 75 mg/kg or 100 mg/kg should be administered when conditions that meet both (B)(i)(c) and (B)(ii) are present in a patient.

As stated previously, the above examples are merely illustrative of the incomplete or conflicting state of the claims, which render the claimed invention as a whole indefinite. Since the efaproxiral sodium dosage must be chosen from applicant's claim-recited conditions, incomplete or conflicting conditions for selecting the dosage render the claims indefinite.

The following comment applies to claim 2, part (B)(iii)(c). This part of the claim states that SpO_2 was ≥93% "on the previous dosing day that led to holding efaproxiral." While this does not rise to a level of indefiniteness that warrants a rejection, it is nonetheless somewhat confusing. The conditional clause in this part seems unusual in that it requires a very good SpO_2 but the dose was withheld. Although the clause can be understood, the concept behind this step does not make sense. Explanation or rewriting is suggested.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Steffen et al. and Kavanagh in view of Teicher et al. and Chang et al.

Steffen et al. disclose RSR13 as the sodium salt of efaproxiral (first paragraph on pages 249-250), which decreases tumor hypoxic fraction and increases tumor oxygenation (page 251, first full paragraph). Greater than 50% improvement in mean survival is reported in brain metastases patients treated with RSR13 and whole-brain radiation therapy (page 252, second full paragraph). Carbogen breathing + RSR13 administration decreased tumor hypoxic fraction compared to air breathing + RSR13 (page 251, first full paragraph and Figure 2).

Kavanagh et al. establish the well-known concept in the art that improved O_2 delivery to tumors could overcome treatment failures in radiotherapeutic management of solid tumors (first paragraph of the article on pages 1133 to 1134). Kavanagh et al. teach that RSR13 mediates radiosensitization when administered in concert with high O_2 content breathing gas (page 1134, right column, first paragraph). RSR13 functions by reducing hemoglobin-oxygen affinity in human red blood cells and thereby increasing

oxygen delivery to hypoxic tissues (page 1134, left column, first two full paragraphs). Doses of 75 mg/kg and 100 mg/kg for 10 days have been clinically tested to be sufficiently safe (page 1137, see in particular Table 2 and last paragraph of right column; page 1135, left column; page 1136, Table 1). Both i.p. and i.v. administration of RSR13 are disclosed (page 1134, left column, second paragraph, right column, first paragraph). 20-40 Gy in 10-15 fractions over a 2-3 week period is disclosed (page 1134, left column, last paragraph). Combination of RSR13, supplemental oxygen, and radiation therapy is disclosed (e.g., Figure 1 on page 1135). Ongoing Phase II and III studies of treating brain metastases are disclosed (page 1138, right column, last paragraph).

Teicher et al. disclose breathing carbogen, which is 95% O_2, with RSR13 administration "markedly increased tumor oxygenation" (page 5, left column, last paragraph & page 6, Figure 2; see also page 10, left column, last sentence of first paragraph). RSR13 dose of 100 mg/kg to 200 mg/kg (page 5, Table 1) is reported to decrease the number of lung metastases with further decrease obtained by combining RSR13 with radiation therapy (paragraph bridging pages 6-7). RSR13 dose of 50, 100 and 200 mg/kg in combination with fractionated radiation therapy is disclosed (page 7, left column, first full paragraph). Various fractionation schedules are disclosed, including 5 X 3 Gy, 5 X 4 GY (Tables 2 and 3 on page 8). RSR13 administration is disclosed to augment the anticancer efficacy of both radiation therapy and chemotherapy especially in its activity against systemic disease (page 10, left column,

bottom of first full paragraph).

The article by Chang et al. is cited to establish that whole brain radiotherapy is considered standard treatment for patients with brain metastases – on occasion, "a robust response" of multiple brain metastases from breast cancer can be observed" (page 400, paragraph bridging the two columns). A frequently prescribed regimen used in the U.S. to treat brain metastases is 30 GY in 10 fractions, "but the factionation schedule should be tailored to patient prognosis so that late toxicity of WBRT can be minimized in long-term breast cancer survivors" (page 400, right column, first paragraph). Various alternative fractionation schedules such as 10 2.5-Gy, 10 3-Gy, 12 2.5-Gy, 15 2-Gy are disclosed (page 401). RBC concentration of RSR13 after 100 mg/kg dose was 459 microgram per ml (page 1136, left column, last sentence; see also Figure 2).

While the cited references do not *specifically* disclose in one single embodiment the combined administration of radiation, efaproxiral sodium and supplemental oxygen to a host having a CNS metastatic cancer, the combination of the cited references fairly suggests the same. Steffen et al. disclose greater than 50% improvement in mean survival of brain metastases patients treated with RSR13 and whole-brain radiation therapy (page 252, second full paragraph). What appears to be missing in the prior art disclosure is an *explicit* disclosure of supplemental oxygen administration in a CNS metastatic cancer patient, who is receiving radiation and RSR13 therapy. However, the motivation to supply the supplemental oxygenation is found in both Steffen's and

Kavanagh's disclosures wherein 95% O_2 and other high O_2 content breathing administered in concert with RSR13 increases tumor oxygenation, which would make the tumor cells more susceptible to radiation therapy.

Applicant's rather complicated claim schematic for efaproxiral sodium dosage is noted. Basically, the choices are 0 mg/kg, 75 mg/kg or 100 mg/kg. To simplify this discussion, step (B)(i)(a) of claim 2 is noted for illustration. Given the prior art suggestion of 100 mg/kg efaproxiral dosage and 95% oxygen supplementation for cancer treatment, the same dosage for radiation treatment day 1 for a male patient of less than 95 kg and supplemental oxygen of 93% or higher would have been obvious. To simply the discussion of claim 3, step (B)(i)(a) is noted for illustration. Given the prior art suggestion of 75 mg/kg efaproxiral dosage and 95% oxygen supplementation for cancer treatment, the same dosage for radiation treatment day 1 for a breast cancer patient with CNS metastatic cancer and supplemental oxygen of 90% or higher would have been obvious. Creatinine level of 2.0 mg/dL or less would have been also obvious since a level higher than that would indicate a serious kidney malfunction to the ordinary skilled artisan in this field, which would necessitate stoppage of treatment to address such complications.

Applicant's claim 4 feature of at least about 3 Gy fractions at least once every day for 10 days would have been suggested from the frequently prescribed regimen in the U.S. of 30 Gy in 10 fractions, as well as the recognition by the ordinary skilled person in this art that the particular fractionation schedule for a patient must be tailored

to patient prognosis and response. Similarly, at least about 30 Gy of radiation would have been obvious from the need to more aggressively treat the cancer in certain patients and also from the disclosure of up to 40 Gy by Kavanagh et al.

Achieving an efaproxiral sodium RBC concentration of greater than about 483 microgram/ml is merely another way of requiring greater than about 100 mg/kg RSR13 because Kavanagh et al. show that 100 mg/kg provides a RBC concentration which is slightly lower than that. It is noted that RSR13, i.e. efaproxiral sodium, dose of greater than 100 mg/kg would have been fairly suggested by similar doses disclosed by the cited references and also from recognition by the ordinary skilled artisan in this field to tailor the dose to the particular patient profile and prognosis.

All other claim features are already addressed by the specific teachings of the cited references. Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly disclosed or suggested by the teachings of the cited references.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to JOHN PAK whose telephone number is **(571)272-0620.** The Examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Johann Richter, can be reached on **(571)272-0646**.

The fax phone number for the organization where this application or proceeding is assigned is **(571)273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.

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